



# Monitoring Deferasirox Therapy

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SIDE EFFECT	MONITORING	FREQUENCY	ACTION <sup>#</sup>
<b>Reduced renal function</b>	Serum creatinine	3-4 weeks	<ul style="list-style-type: none"><li>• Lower dose by 25% if &gt;33% increase over baseline at 2 consecutive visits</li><li>• Lower dose by 50% for 1 week if &gt; upper limit of normal (ULN)</li><li>• Increase gradually to previous dose if tolerated.</li><li>• Interrupt therapy if creatinine &gt;2x ULN</li></ul>
<b>Renal tubular dysfunction</b>	Serum potassium, phosphorus and bicarbonate	3-4 weeks	<ul style="list-style-type: none"><li>• Lower dose by 25% if potassium, bicarbonate or phosphorus are &lt; lower limit of normal on 2 consecutive visits</li><li>• Interrupt treatment for 1 week or more for severe deficits</li></ul>
<b>Proteinuria</b>	Urine protein: creatinine ratio (or albumin: creatinine)	3 months	<ul style="list-style-type: none"><li>• Confirm any urine dipstick 2+ or higher with spot urine protein:creatinine or albumin:creatinine ratio</li><li>• If urine protein: creatinine ratio &gt;0.5 g/g (or albumin:creatinine &gt;300 mg/g) on 2 consecutive samples one month apart, lower dose by 50% and consider nephrology evaluation</li><li>• Explore alternative causes for proteinuria</li></ul>
<b>Elevated transaminases, but normal at baseline</b>	Alanine aminotransferase (ALT)	3-4 weeks	<ul style="list-style-type: none"><li>• Lower dose by 25% if ALT&gt;3x ULN on 2 consecutive visits</li><li>• Interrupt therapy if ALT&gt;10x ULN or direct bilirubin &gt;2x ULN</li><li>• Explore alternative causes for elevated ALT</li></ul>
<b>Elevated transaminases at baseline</b>	Alanine aminotransferase (ALT)	3-4 weeks	<ul style="list-style-type: none"><li>• Lower dose by 50% in individuals with chronic viral hepatitis or marked liver iron burden if further elevation in ALT (&gt;2x from baseline value and &gt;5x ULN) on 2 consecutive visits (see literature review)</li><li>• If ALT does not improve after one month of holding DFX, the higher dose may be resumed</li></ul>
<b>Retinopathy</b>	Retinal examination	12 months	<ul style="list-style-type: none"><li>• Specialty evaluation to rule out alternative etiology if abnormal</li></ul>
<b>Drug interactions</b>	Concomitant drugs	3-4 weeks	<ul style="list-style-type: none"><li>• Evaluate potential interaction with initiation of any new drug (see literature review)</li></ul>

**#Action:** Consultation with a comprehensive thalassemia center is recommended if a toxicity is recurrent or causes interruption of treatment

Deferasirox (DFX) is available in three formulations: deferasirox dispersible tablets (Exjade), deferasirox tablets (Jadenu tablets) and deferasirox granules (Jadenu Sprinkle). Guidance for monitoring of deferasirox therapy is derived from clinical trials, case reports, and FDA-approved prescribing information. Monitoring the toxicity of chelation drugs is essential for patient safety and treatment efficacy in the long term. Regular monitoring increases the likelihood that chelation therapy will not require dose interruption. Some toxicities are independent of iron burden, while others may be more frequent with low iron burden. The risk of toxicity also varies with age, diagnosis, intercurrent illness, and baseline organ function.

Individuals starting on deferasirox should be monitored for skin rash and gastro-intestinal symptoms. Deferasirox should be stopped if skin rash develops, but can be reintroduced at a lower dose with oral steroids given for 2-3 weeks. Severe skin reactions, such as Stevens-Johnson syndrome and erythema multiforme should result in permanent discontinuation of the drug. The GI adverse events are less frequent with Jadenu tablet than with Exjade DT, which have included pain, diarrhea and bloating. Uncommon, but serious side effects of DFX are serious GI bleeding (ulceration or perforation), hepatic toxicity (including hepatic failure), renal toxicity (including acute renal failure), renal tubular acidosis (Fanconi's syndrome), and cytopenias (particularly with preexisting bone marrow disorders). Elderly patients are more susceptible to serious adverse reactions. It is recommended to hold deferasirox for a few days during any febrile or diarrheal illnesses.

### Summary of Literature Review:

Jadenu contains the same active ingredient as Exjade, and the two are similar except that Jadenu has 36% greater bioavailability and 30% higher peak serum concentrations.<sup>1</sup> The dose of Jadenu is 70% of comparable Exjade dose, which is an important consideration when patients switch between formulations. The bioavailability and peak and trough serum concentration of DFX are increased when it is taken with fat-containing meal,<sup>2</sup> though this has not been observed to change the frequency of side effects.<sup>3</sup>

A common side effect of Exjade is gastrointestinal discomfort in up to one-third of individuals manifesting as nausea, abdominal pain or diarrhea.<sup>4-11</sup> These side effects appear to be less with Jadenu from experience and supported by patient-reported outcomes in a study.<sup>4</sup> A serious side effect of deferasirox is occurrence of GI hemorrhage. GI bleeding is believed to be more common in elderly patients with thrombocytopenia secondary to malignancies, and its use in such cases is contra-indicated if platelet count is  $<50 \times 10^9/L$ . Cases of bleeding from gastric or duodenal ulcer in individuals with thalassemia lacking these risk factors are rare but serious.<sup>5-8</sup>

A minority of patients experience elevation in transaminases during DFX treatment,<sup>6,9-11</sup> although the true incidence is

unknown as severe iron overload also causes hepatic inflammation. Establishing baseline liver function is important (particularly when liver iron concentration exceeds 15 mg/g dry weight) to avoid unnecessary reductions in dose. The larger studies have reported persistent elevated alanine transaminase (ALT) in 1-6% of patients on DFX treatment. These elevations were usually mild, but 1-3% of patients experienced increase in serum ALT levels over ten times the upper limit.<sup>11</sup> Cholestasis is reported in an occasional patient,<sup>6</sup> but is very rare. Deferasirox is contraindicated in patients with severe liver disease (Child-Pugh C), and should be administered at a 50% reduced dose in those with moderate (Child-Pugh B) dysfunction.<sup>12</sup>

In clinical practice, the most frequently encountered toxicity of DFX is renal dysfunction. This can take various forms, including elevated creatinine, proteinuria and proximal tubular dysfunction. The use of DFX is contraindicated in patients with creatinine clearance  $<40$  ml/min.<sup>12</sup> Increase in serum creatinine is relatively frequent and may require reduction in dose. The incidence of transient creatinine elevation is 32-38% in clinical trials,<sup>13,14</sup> with dose reduction in 13% of subjects.<sup>14</sup> Acute renal failure can develop if the dose is not modified, though its incidence is  $<1\%$ .<sup>13</sup> Proteinuria occurs in 6% cases but the need for dose reduction due to persistent high-level proteinuria is rare.<sup>10,15,16</sup> Tubular dysfunction or Fanconi's syndrome, manifesting as urinary electrolyte wasting and glycosuria, has been described in multiple case reports,<sup>17-23</sup> with an incidence of 8% in one clinical trial,<sup>24</sup> but rare in others.<sup>13</sup> Tubular dysfunction is more common in pediatric patients with relatively low body iron.<sup>12</sup> The occurrence of febrile infection and dehydration, such as from diarrheal illness, can uncover or increase severity of acidosis that may require urgent attention. Low serum phosphorus and potassium are commonly described in this setting.<sup>21,22</sup>

Skin rash can occur at the beginning of treatment with DFX in 4-17% of patients,<sup>14,25,26</sup> but is transient in most cases, allowing continuation of therapy with or without a brief interruption. In post-marketing experience, Stevens-Johnson syndrome, toxic epidermal necrolysis, alopecia, anaphylactic reactions, vasculitis and angioedema have been reported.<sup>12</sup> Severe immune or cutaneous reactions preclude further therapy. Other rarely seen side effects are lenticular opacities and, possibly, hearing loss.<sup>6,27,28</sup> Deferasirox is contraindicated during pregnancy and lactation. Deferasirox may interact with other drugs due to its effect on cytochrome P450 enzymes (such as induction of CYP3A4 and CYP2C8), and its metabolism by UDP-glucuronosyltransferase (UGT). A complete list of these agents is available with deferasirox prescribing information and through programs to analyze drug interactions.

*References for this checklist can be found online at the Cooley's Anemia Foundation's website:*

[www.thalassemia.org/checklists-references](http://www.thalassemia.org/checklists-references).

*The Cooley's Anemia Foundation encourages doctors to utilize this information in treating thalassemia patients.*

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